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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/JP99/04978 (22) International Filing Date: 10 September 1999 (10.09.99) (30) Priority Data: PP 5841 14 September 1998 (14.09.98) AU (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): YAMAMOTO, Nobuchika [JP/JP]; 17-10-303, Mukomotomachi 1-chome, Amagasaki-shi, Hyogo 661-0043 (JP). YAMAZAKI, Harumi [JP/JP]; 1882-26, Shimoinayoshi, Chiyodamachi, Niihari-gun, Ibaraki 315-0052 (JP). ISHIKAWA, Takeshi [JP/JP]; 3-6-6-602, Kaminoshima-cho, Amagasaki-shi, Hyogo 661-0014 (JP). JOHKEI, Shigeru [JP/JP]; 2-1-13-1203, Koishikawa, Bunkyo-ku, Tokyo 112-0002 (JP). SAKAI, Fumio [JP/JP]; 6-7, Ninomiya 2-chome, Tsukuba-shi, Ibaraki 305-0051 (JP).		(74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP). (81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: NEW USE		
(57) Abstract A new use of immunosuppressant for treating or preventing MMP-mediated diseases is provided.		

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PP 5841**14 September 1998 (14.09.98) AU**(71) Applicant (for all designated States except US): **FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).**

(72) Inventors; and

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(88) Date of publication of the international search report:

13 July 2000 (13.07.00)(54) Title: **NEW USE OF IMMUNOSUPPRESSANTS FOR MMP-MEDIATED DISEASES**

(57) Abstract

A new use of immunosuppressant for treating or preventing MMP-mediated diseases is provided. The preferred immunosuppressants are tacrolimus, cyclosporin A or 33-epi-chloro-33-desoxyascomycin (pimecrolimus). Particularly, preferable MMP-mediated diseases are the diseases or conditions caused by gelatinase and/or collagenase, and/or inflammatory diseases concerned with gelatinase; such as arthritis (e.g., osteoarthritis, rheumatoid arthritis, etc.), cerebral diseases (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastric ulceration, etc.), abnormal wound healing, periodontal diseases, bone diseases (e.g., Paget's diseases, osteoporosis, etc.), tumor growth, tumor metastasis or invasion, HIV-infection, decubitus, decubitus ulcer, restenosis, epidermolysis bullosa, sepsis, septic shock, neoplasm, psoriasis, neovascularization and multiple sclerosis.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/04978

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/435 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KATO, TAKASHI: "Effect of immunosuppressant drug (FK 506 and cyclosporin) on gingival fibroblasts" NIPPON SHISHUBYO GAKKAI KAISHI (1995), 37(2), 211-223, 1995, XP000905245 abstract	1-9
X	TOCCI, MICHAEL J. ET AL: "The immunosuppressant FK506 selectively inhibits expression of early T cell activation genes" J. IMMUNOL. (1989), 143(2), 718-26, 1989, XP000906772 abstract	1-9
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

2 May 2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARITA, C. ET AL: "Inhibition by FK506 of established lesions of collagen-induced arthritis in rats" CLIN. EXP. IMMUNOL. (1990), 82(3), 456-61 ,1990, XP000904902 abstract	1-9
X	KOCH, K. ET AL: "CP-123,369: a potent, orally active immunosuppressive agent" INFLAMMATION RES. (1995), 44(SUPPL. 2), S183-S184 ,1995, XP000904905 the whole document	1-9
X	SUGIYAMA, EIJI ET AL: "FK506, an immunosuppressant, partially inhibits interleukin 6 production by adherent rheumatoid synovial cells" J. RHEUMATOL. (1994), 21(9), 1597-601 , 1994, XP000904906 abstract	1-9
X	GRIFFITHS, R. J. ET AL: "Characterization of passively transferred antigen arthritis induced by methylated bovine serum albumin in the rat: effect of FK 506 on arthritis development" AGENTS ACTIONS (1992), 36(1-2), 146-51 , 1992, XP000904904 abstract	1-9
X	ZENIYA, AKIRA ET AL: "Anti- ulcer effect of FK 506, immunosuppressive agent, in rats" J. GASTROENTEROL. (1994), 29(3), 383-4 , 1994, XP000904975 the whole document	1-9
X	WO 91 17754 A (FUJISAWA PHARMACEUTICAL CO) 28 November 1991 (1991-11-28) abstract page 2, line 5-29 page 5, line 1 -page 11, line 11; claims 1-19	1-9
X	KARASHIMA, TADASHI ET AL: "FK 506 and cyclosporin A inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the G0/G1 phases of the cell cycle" J. DERMATOL. SCI. (1996), 12(3), 246-254 , 1996, XP000904978 abstract	1-9
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No.

JP 99/04978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MROWIETZ, U. ET AL: "The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion" BR. J. DERMATOL. (1998), 139(6), 992-996 , 1998, XP000904979 abstract; figure 1	1-7
X	BUTCHER, STEVEN P. ET AL: "Neuroprotective actions of FK506 in experimental stroke: in vivo evidence against an antiexcitotoxic mechanism" J. NEUROSCI. (1997), 17(18), 6939-6946 , 1997, XP000904977 abstract	1-9
X	INABA, HIROYUKI ET AL: "Effect of indomethacin and tacrolimus hydrate on the healing process of experimental gastric ulcers of rats created by mucosal resection: course of changes in the interleukin-1.beta. (IL-1.beta.) expression" SEI MARIANNA IKA DAIGAKU ZASSHI (1998), 26(5), 555-563 ,1998, XP000905128 abstract	1-9
X	SANDBORN, WILLIAM J.: "Preliminary report on the use of oral tacrolimus (FK506) in the treatment of complicated proximal small bowel and fistulizing Crohn's disease" AM. J. GASTROENTEROL. (1997), 92(5), 876-879 ,1997, XP000905061 abstract	1-9
X	HISANAGA ET AL: "Implication of nitric oxide synthase activity in the genesis of water immersion-stress induced gastric lesions in rats: the protective effects of FK-506" ALIMENTARY PHARMACOLOGY & THERAPEUTICS, GB, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, vol. 10, no. 10, 1996, pages 933-940-940, XP002108980 ISSN: 0269-2813 abstract	1-9
X	WO 98 11908 A (BRITISH BIOTECH PHARM ;WOOD LARS MICHAEL (GB); WRIGHT ANNETTE (GB)) 26 March 1998 (1998-03-26) abstract page 6, paragraph 4 -page 8, paragraph 2 page 15, paragraph 2; claims 1-8	1-9
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 99/04978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 18048 A (PFIZER) 16 September 1993 (1993-09-16) abstract page 2, line 10 -page 5, line 23 _____	1-7
X	WO 93 18050 A (PFIZER) 16 September 1993 (1993-09-16) page 2, line 11 -page 6, line 10 _____	1-7
X	DE 43 29 503 A (GALENIK LABOR FREIBURG GMBH) 2 March 1995 (1995-03-02) abstract; claims 1-6 _____	1-9
X	US 5 352 671 A (BAUMANN KARL ET AL) 4 October 1994 (1994-10-04) abstract column 25, line 49 -column 26, line 60; example 66A column 1, line 5 _____	1-9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/04978

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4, 6, 9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 4, 6, 9
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ N protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7,9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically mentioned in the claims, with due regard to the general idea underlying the present application.

Present claims 1-9 relate to compounds defined by reference to a desirable characteristic or property, namely immunosuppressant property. The claims cover all compounds/uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the claims.

The Present claims 1-9 relate to a method/use defined (inter alia) by reference to the following parameter(s):

P1: MMP production inhibitor/ treating MMP-mediated disease.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the "More preferable MMP-mediated diseases" (Cf. page 15 of the description), with due regard to preferable MMP-mediated diseases.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Original Application No

PCT/JP 99/04978

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9117754	A	28-11-1991	NONE	
WO 9811908	A	26-03-1998	AU 4390597 A EP 0936918 A	14-04-1998 25-08-1999
WO 9318048	A	16-09-1993	AT 159725 T CA 2131373 A DE 69314947 D DE 69314947 T DK 636136 T EP 0636136 A ES 2108261 T FI 944015 A GR 3025672 T JP 7500350 T JP 2562001 B US 5631235 A	15-11-1997 16-09-1993 04-12-1997 05-03-1998 22-12-1997 01-02-1995 16-12-1997 01-09-1994 31-03-1998 12-01-1995 11-12-1996 20-05-1997
WO 9318050	A	16-09-1993	AT 153027 T CA 2131372 A,C DE 69310721 D DE 69310721 T DK 629209 T EP 0629209 A ES 2102642 T FI 944017 A GR 3024048 T JP 2563080 B JP 7500352 T MX 9301060 A US 5747465 A	15-05-1997 16-09-1993 19-06-1997 04-09-1997 13-10-1997 21-12-1994 01-08-1997 01-09-1994 31-10-1997 11-12-1996 12-01-1995 01-09-1993 05-05-1998
DE 4329503	A	02-03-1995	AU 693470 B AU 7535494 A CA 2170748 A WO 9506464 A EP 0716598 A JP 9501939 T NZ 271655 A	02-07-1998 22-03-1995 09-03-1995 09-03-1995 19-06-1996 25-02-1997 22-09-1997
US 5352671	A	04-10-1994	US 5912238 A AT 126803 T AU 640963 B AU 6584390 A CA 2029694 A DE 69021833 D DE 69021833 T DK 427680 T EP 0427680 A ES 2077663 T GR 3017858 T HK 30096 A HU 210900 B IE 69974 B IL 96268 A JP 2750302 B JP 3223291 A KR 166074 B	15-06-1999 15-09-1995 09-09-1993 23-05-1991 10-05-1991 28-09-1995 21-03-1996 18-12-1995 15-05-1991 01-12-1995 31-01-1996 23-02-1996 28-09-1995 16-10-1996 23-07-1996 13-05-1998 02-10-1991 15-01-1999

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5352671 A		LV 11621 A	20-12-1996
		LV 11621 B	20-04-1997
		NZ 235991 A	26-05-1993
		ZA 9009024 A	29-07-1992